CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40263

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? NO
If no, list why:

Container Labels:(2 mL and 10 mL);

Carton Labeling:(1 x 2 mL and 1 x 10 mL)

Professional Package Insert Labeling:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Methotrexate Sodium Injection

NDA Number: 11-719/S-095
NDA Drug Name: Methotrexate Sodium Injection
NDA Firm: Lederle Laboratories

Date of Approval of NDA Insert and supplement #:
Approved May 20, 1997; Revised January 25, 1990.
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Labels in file folder and labels submitted in the side-by-side review.

Basis of Approval for the Carton Labeling: Labeling in file folder and labeling submitted in the side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?		X	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Methotrexate Sodium Injection; Lederle Laboratories; Approved May 20, 1997; Revised January 25, 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light.

   AND: Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until contents are used.

   USP: Preserve in single-dose or in multiple dose containers preferably of glass, protected from light.

4. Product Line:

   The innovator markets their product in vials containing 50 mg and 250 mg preserved isotonic liquid solution.

   The applicant proposes to market their product in 50 mg and 250 mg preserved isotonic liquid solution.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 141, Vol. 1.1.

6. All manufacturing will be performed by Bigmar. All outside firms are utilized for testing. See pages 301 and 324, Vol. 1.1.

7. Container/Closure:

   This product will be packaged in clear glass with grey rubber stoppers and aluminum seals with an orange flip off cap. See pages 1300, 1307 and 1312, Vol. 1.3.

8. This description of the finished dosage form "is a clear solution". Page 1431.

9. The innovator has a shared insert for three dosage forms - Tablets, Injection and For Injection. Several sections of the package insert were revised to exclude information pertaining to Rheumatoid Arthritis and the PO dosage form. The PO form, according to the D&A section is only indicated in the treatment of rheumatoid arthritis. The guidance document from 1988 also had this information deleted.

Date of Review: **November 10, 1998**

Date of Submission: **October 29, 1998**

Reviewer: /S/ **Date:** 11/18/98

Team Leader: /S/ **Date:** 11/18/98

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cc:

ANDA 40-263
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace 11-10-98 (no cc)
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Review

ANDA Number: 40-263

FIRM: Bigmar Inc._DOSAGE FORM: Methotrexate Injection USP (Preserved).

STRENGTH 25mg/mL, 2 mL and 10 mL fills in a 10 mL vial.

CGMP STATEMENT/EER UPDATE STATEMENT:

EER pending.

BIO STUDY: Waiver granted 12/31/97

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

Not applicable. Both drug substance and drug product are USP.

STABILITY - ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION

Yes. Container section described a 10 mL clear glass vial with rubber cap and aluminum seal.

Tentative Expiration date is 24 months (2 years).

LABELING:

FPL found adequate on 1/14/99.

STERILIZATION VALIDATION (IF APPLICABLE):

Sterilization validation found adequate on 2/2/99.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.)

No bio batch (waiver granted 12/29/97).

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED BY THE SAME PROCESS?)

Liters

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Liters (Manufactured in the same manner as stability batch).

/S/ 2/17/99

Prepared by Stephen Sherken on 2/8/99

/S/ 2/18/99

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 40-263

3. NAME AND ADDRESS OF APPLICANT

Bigmar Inc.
Johnstown, OH 43031-9141

4. LEGAL BASIS FOR SUBMISSION

505(j), 21 CFR 314.94

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Methotrexate Injection USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

DOA 7/28/97; Amend 9/17/97; Amend (Chemistry-Vol 2.1 (Micro-Vol 2.2) 12/17/97; NA (Chem Major) 2/2/98; Amend 2/9/98; Amend (Chem Major) Vol. 2.1, 2/16/98; Amend (Micro), Vol 3.1, 5/29/98; NA (Micro) 6/10/98; Amend (Chem) 6/11/98; NA (Fax) 8/6/98; NC 9/5/98 (Includes Chem, Micro and Labeling); Label Reviewed & Faxed 9/16/98; Micro reviewed 9/21/98; Amend 9/26/98 (Label FAX); Label Reviewed 10/7/98; NA with micro attachment, 10/23/98; *Label Amend 10/29/98; Label Review 11/18/98; *Fax Amend 11/20/98; Micro review 12/18/98; *Label Amend 11/30/98. *=new submissions

10. PHARMACOLOGICAL CATEGORY

Neoplastic Diseases

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 11-719, DMF

13. DOSAGE FORM

Clear colorless solution.

14. POTENCY

25 mg/mL in 2, and 10 mL fills in 10 mL vials (preserved).

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS N/A

17. COMMENTS

Excellent application.

No chemistry deficiencies remaining.

Third sterility assurance review performed for the 11/20/98 amendment on 12/18/98. Fax deficiencies remain.

Bio-waiver was granted on 12/31/97.

EER recommends withhold by M. Egas on 6/3/98 for Bigmar's facility in Barbing, Switzerland.

Labeling review of 11/30/98 amendment pending.

18. CONCLUSIONS AND RECOMMENDATIONS

FAX to Bigmar because of Micro deficiencies.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken 12/21/98

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commercial

information

Chemistry Review #4

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 40-263

3. NAME AND ADDRESS OF APPLICANT

Bigmar Inc.
Johnstown, OH 43031-9141

4. LEGAL BASIS FOR SUBMISSION

505(j), 21 CFR 314.94

5. SUPPLEMENT(s)	6. PROPRIETARY NAME
N/A	N/A
7. NONPROPRIETARY NAME	8. SUPPLEMENT(s) PROVIDE(s) FOR:
Methotrexate Injection USP	N/A

9. AMENDMENTS AND OTHER DATES:

DOA 7/28/97; Amend 9/17/97; Amend (Chemistry-Vol 2.1 (Micro-Vol 2.2) 12/17/97; NA (Chem Major) 2/2/98; Amend (Chem Major) Vol. 2.1, 2/16/98; Amend (Micro), Vol 3.1, 5/29/98; NA (Micro) 6/10/98; Amend (Chem) 6/11/98; NA (Fax) 8/6/98; NC 9/5/98 (Includes Chem, Micro and Labeling); Label Reviewed & Faxed 9/16/98; Micro reviewed 9/21/98; Amend 9/25/98 (Label FAX); Label Reviewed 10/7/98; NA with micro attachment, 10/23/98; Label Amend 10/29/98; Label Review 11/18/98; Fax Amend 11/20/98; Micro review 12/18/98; Label Amend 11/30/98; Chem review #4 & Fax deficiencies 12/24/98; Amend (FPL) 1/8/99; RPL Rec approval 1/14/99; Amend (Micro) 1/21/99; NC (Micro) 1/27/99, Micro review recommends approval 2/2/99

10. PHARMACOLOGICAL CATEGORY	11. Rx or OTC
Neoplastic Diseases	Rx

12. RELATED IND/NDA/DMF(s)

NDA 11-719, DMF

13. DOSAGE FORM	14. POTENCY
Clear colorless solution.	25 mg/mL in 2, and 10 mL fills in a 10 mL vial (preserved).

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS N/A

17. COMMENTS

No chemistry deficiencies remaining.

Fourth sterility assurance review performed for the Amendments of 1/21/99 & 1/27/99 recommended approval on 2/2/99.

Bio-waiver was granted on 12/31/97.

EER recommends withhold by M. Egas on 6/3/98 for Bigmar's facility in Barbing, Switzerland. FUR is pending.

FPL reviewed for Label amendment 1/8/99 on 1/14/99. No Deficiencies found. Recommended approval.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend approval pending adequate EER.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken 2/8/99

cc: ANDA 40-263
Division File
Field Copy

Endorsements:

/S/ 2/17/99

HFD-625/SSherken/2/9/99
HFD-625/Msmela/2/10/99
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F/t by: gp/2/16/99

/S/ 2/18/99

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Chemistry Review #5